Lack of association between Helicobacter pylori infection and extracardiac atherosclerosis in dyspeptic elderly subjects

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Abstract

Background: there are conflicting data on the association between Helicobacter pylori (HP) infection and cardiovascular diseases.

Aim: to determine if there is an association between gastric HP infection and atherosclerosis of cerebral or peripheral arteries in elderly subjects.

Methods: 90 dyspeptic elderly subjects had upper gastro-intestinal endoscopy and the gastroduodenal pathology was identified. HP infection was confirmed by gastric histology and the rapid urease test. Vascular ultrasonography of extracranial cerebral arteries and leg arteries was performed to evaluate (i) the presence of an atherosclerotic lesion, (ii) the total length of all plaques documented and (iii) the number of arteries with atherosclerotic lesions. Statistical analysis was by the χ² test, Yates's corrected χ² test, the Mann–Whitney test and logistic regression.

Results: 59 subjects were HP-positive. These had a higher prevalence of peptic ulcer disease (P = 0.01) and higher serum levels of IgG anti-HP antibodies (P = 0.0001), but no significant differences in the number of atherosclerotic lesions, the total length of the plaques or the number of arteries with lesions. No significant association of HP positivity was found with diabetes mellitus, hypertension, cigarette smoking or coronary heart disease, nor with serum concentrations of HDL-cholesterol, fibrinogen, triglycerides or glucose.

Conclusions: elderly dyspeptic subjects with gastric HP infection had significantly more peptic ulcer disease but no more atherosclerotic lesions than those who were HP-negative. Atherosclerosis was not associated with HP infection. In this cross-sectional study of elderly patients with dyspepsia, no association between HP infection and extracardiac atherosclerosis was found.

Keywords: atherosclerosis, elderly, Helicobacter pylori

Introduction

Chronic Helicobacter pylori (HP) infection may be associated with a higher incidence of coronary heart disease [1–4]. The mechanisms postulated include an increase of plasma fibrinogen [5, 6] or a modification of the serum lipid profile [7] associated with the long-term effects of HP infection (as also suggested for Chlamydia pneumoniae [8]). However, conflicting data exist on the effect of HP infection on serum fibrinogen concentrations [9, 10], and a lack of association between HP infection and coronary heart disease has been reported [11].

There are few studies of the association between HP infection and extracardiac atherosclerosis. No convincing evidence for, or against, a causal association between HP infection and vascular diseases has been provided [12].

The aim of our study was to determine if there is an association between gastric HP infection and...
Atherosclerosis of cerebral or peripheral arteries exists in elderly dyspeptic patients.

Materials and methods

Patients

Patients were recruited prospectively from the endoscopy unit of the Geriatric Department in Vicenza, Italy. Initially, 134 consecutive dyspeptic subjects over 65 who had had upper gastro-intestinal endoscopy were screened, of whom 44 patients were excluded because of gastric cancer (nine patients), previous major gastrointestinal surgery (two patients), the inability to obtain gastric biopsies during endoscopy (15 patients), concomitant or previous treatment with antibiotics, proton pump inhibitors (omeprazole, lansoprazole, pantoprazole), H2-blockers or HP-eradication therapy in the preceding 4 weeks (eight patients). An additional two patients with haematological disorders and eight with other severe concomitant diseases were also excluded. The study was therefore of 90 elderly patients, 40 of whom were men. Their mean age was 78.2 years (range 65–91).

Diagnosis of HP infection

All patients included in the study underwent upper gastro-intestinal endoscopy. Gastrroduodenal pathology was recorded and HP infection evaluation was conducted in all subjects by means of gastric histology and the rapid urease test. Gastric histology was performed on at least two biopsies from the antrum and two from the body of the stomach. Specimens were immediately fixed in buffered neutral formalin and embedded in paraffin. Sections were stained with haematoxylin and eosin and modified Giemsa to detect HP. Biopsies were assessed by one masked pathologist (L.B.) and graded according to the Sydney system classification [13]. The rapid urease test was performed on one biopsy each from the antrum and the body: positivity was assessed according to the manufacturer’s instructions (CLO test, Delta West Pty Ltd, Bentley, Western Australia).

Diagnosis of atherosclerosis

After endoscopy, vascular ultrasonography was performed to evaluate extracranial cerebral arterial and leg arteries (anterior and posterior tibial and peroneal) using a high resolution duplex B-mode scanner (SIM7000 CFM, Esaote-Biomedica, Italy) and a continuous wave Doppler scanner (Stereodop 448, Ultrasomed, Italy). Diagnosis of atherosclerosis [14] was based on the presence of an atherosclerotic plaque, defined as a wall lesion with a thickness of >2 mm. The extent of atherosclerotic disease was graded by (i) total length (in mm) of all documented plaques and (ii) the number of peripheral arteries with atherosclerotic lesions (score: 0–6 arteries) [15].

Risk factors for atherosclerosis and serum indices

The presence of diabetes mellitus (i.e. positive history for disease, hypoglycaemic treatment and/or fasting serum glucose higher than 7.7 mmol/l), hypertension (a positive history for disease, anti-hypertensive treatment and/or blood pressure values above 140/90 mmHg), cigarette smoking habit (>10 cigarettes daily) and coronary heart disease (a positive history for angina, myocardial infarct or electrocardiograph-related evidence) were evaluated by subject interviews, general practitioners’ clinical records and clinical assessment. Serum samples were taken to determine the levels of IgG anti-HP antibodies [in Monoclonal Units (MU)/ml; ELISA method, Biolife]. A cut-off point of >20 MU/ml indicated positivity. Serum total cholesterol (mmol/l), HDL-cholesterol (mmol/l), fibrinogen (μmol/l), triglycerides (mmol/l) and glucose (mmol/l) were also determined.

Statistics

The χ² test was used to compare the percentages of prevalence of atherosclerotic plaques, the total length of the atherosclerotic plaques and the number of peripheral arteries with lesions in HP-positive and HP-negative patients. Yates’s corrected χ² test was used to compare the prevalence of gastric pathologies and concomitant vascular risk factors in HP-positive and HP-negative patients and in patients with or without atherosclerosis. The Mann–Whitney test was performed to compare serum values in patients divided according to the presence of HP infection and to the presence of atherosclerosis. Two multivariate analyses (logistic regression) were performed to evaluate the potential role of clinical conditions and serum parameters as risk factors for both HP infection and atherosclerosis disease, calculating the odds ratios with 95% of confidence interval for the single variables. The Biomedical Data Processing package (BMDP-LR) was used with the BMDP default parameters. All P values were two-tailed with statistical significance indicated by a value of P < 0.05.

Results

A total of 59 subjects were HP-positive (27 men, mean age 78.1) and 31 HP-negative (13 men, mean age 77.9). HP-positive patients had a significantly higher prevalence of peptic ulcer disease, less gastritis and fewer negative results at endoscopy compared with HP-negative patients (Pearson χ² = 8.162, P = 0.01).

No significant differences were found between HP-positive and HP-negative patients in the percent-
age of patients with atherosclerotic plaques (70.0% of HP-positive and 70.9% of HP-negative subjects), the total length of the atherosclerotic plaques (22.9 ± 3.4 mm in HP-positive and 20.3 ± 2.3 mm in HP-negative subjects) or the number of peripheral arteries with lesions (53.8% and 35.4% had 0, 42.5% and 32.2% had 1–3, and 23.7% and 32.2% had 4–6). In addition, there was no correlation between HP positivity and the prevalence of diabetes mellitus, hypertension, cigarette smoking or coronary heart disease.

Higher concentrations of total cholesterol ($P=0.035$) and IgG anti-HP antibodies ($P=0.0001$) were found in HP-positive than HP-negative subjects; however, no differences in serum HDL-cholesterol, fibrinogen, triglycerides or glucose were found between the two groups. With logistic regression analysis, none of the instrumental vascular measures or clinical and serological risk factors studied were associated with HP infection.

In 62 patients, extracardiac vascular atherosclerotic lesions were documented by ultrasonography. The prevalence of HP infection was 67.7% in patients with and 60.7% in patients without atherosclerosis. No differences in gastroduodenal pathology were found in patients with or without atherosclerosis (Pearson $X^2 = 1.854, P=0.39$; Table 1).

As expected, we found a higher prevalence of diabetes mellitus ($P=0.02$) and cigarette smoking habit ($P=0.02$) in patients with atherosclerosis. Multivariate analysis with logistic regression demonstrated that diabetes mellitus, hypertension and smoking habit were independently associated with atherosclerosis. None of the other variables (HP infection, peptic ulcer disease, coronary heart disease and serum levels of total cholesterol, HDL-cholesterol, fibrinogen, triglycerides, glucose and IgG anti-HP antibodies) were significantly associated.

### Discussion

The possibility that HP infection is a risk factor for vascular disease has been investigated in several studies [16]. Many are sero-epidemiological studies based on anti-HP antibody measurements in serum, and few have explored the association of HP infection with atherosclerosis of the cerebral or peripheral arteries [12].

In this study, HP infection was diagnosed by histological detection of the bacterium in the gastric mucosa and not by serum anti-HP antibodies. This is a crucial difference in the diagnosis of active HP infection, the persistence of which might be an important step in inducing persistent exposure of arteries to atherogenic insult [12]. In elderly people, the diagnostic role of anti-HP serology is uncertain [17–19]. Our previous studies on elderly people demonstrated both a higher prevalence of HP infection when detected by serology (IgG anti-HP antibodies) in comparison with histology [20] and a relatively low clinical usefulness of serological tests in monitoring patients after HP-eradication therapy [21]. These observations were confirmed in the present study, in which 17 of 51 HP-negative patients had positive IgG anti-HP antibody levels, i.e. a titre >20 MU/ml. Given these findings and that the $^{13}$C-urea breath test has not yet been validated for elderly subjects, the histological evaluation of the gastric mucosa for bacterium positivity (possibly in conjunction with the rapid urease test) remains the most accurate and consistent diagnostic test for persistence of active HP infection.

Only two studies have explored the relationship between HP infection and extracardiac atherosclerosis. The first [22] showed a positive relationship between HP infection (evaluated by serology) and the risk of stroke in middle-aged patients. However, this

### Table 1. Epidemiological and clinical characteristics of subjects with and without atherosclerosis diagnosed by vascular ultrasonography

<table>
<thead>
<tr>
<th>Atherosclerosis</th>
<th>Positive</th>
<th>Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects</td>
<td>All 62</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>Male 29</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Female 33</td>
<td>18</td>
</tr>
<tr>
<td>Mean age (range)</td>
<td>80.04 (65–91)</td>
<td>74.17 (65–88)</td>
</tr>
<tr>
<td>No. (and %) of subjects with</td>
<td>Peptic ulcer 27 (43.5%)</td>
<td>8 (28.57%)</td>
</tr>
<tr>
<td></td>
<td>Gastritis 53 (53.2%)</td>
<td>19 (67.85%)</td>
</tr>
<tr>
<td></td>
<td>Negative endoscopy 2 (3.2%)</td>
<td>1 (3.57%)</td>
</tr>
</tbody>
</table>

*Pearson $X^2 = n.s.$
association disappeared after adjustment for social class and other cardiovascular risk factors. The second [23] showed no evidence of the presence of HP bacteria, evaluated by polymerase chain reaction, in plaque specimens from 51 patients (mean age = 68.3 years) who underwent surgery for abdominal aortic aneurysm. In the present study, atherosclerosis was investigated using vascular ultrasonography for diagnosis and quantification of vascular wall lesions with a thickness of ≥2 mm in the extracranial cerebral or leg arteries. The use of vascular ultrasonography has been recommended as the most clinically useful, non-invasive method for evaluating atherosclerosis [14, 15].

Our results show that elderly patients with HP infection had, as expected, a higher prevalence of peptic ulcer disease and higher titres of IgG anti-HP antibodies. These findings were in agreement with recent studies demonstrating that, in elderly subjects, HP infection is associated with clinically important gastroduodenal pathologies [24, 25]. HP eradication reduces both short- and long-term symptomatology, gastritis activity and ulcer recurrences [26, 27].

HP-positive patients did not have a higher prevalence for atherosclerotic lesions or clinical risk factors for vascular diseases than HP-negative subjects. Logistic regression analysis demonstrated a lack of association between HP infection and all instrumental, clinical and serological risk factors for atherosclerosis. Moreover, the prevalence of coronary heart disease did not differ between HP-positive and HP-negative subjects. This finding contrasts with other studies which have reported an association between chronic HP infection and higher incidence of coronary heart disease [1–4]. One explanation is that ours is a cross-sectional study of an elderly population. Morbidity and mortality due to coronary heart disease in young or middle age could have selected out the population of this study, decreasing the observed number of subjects with coronary heart disease. In support of this hypothesis, an association between HP infection and coronary heart disease was reported to be stronger in young patients [3], and a recent cross-sectional prospective survey of an elderly Finnish population [28] showed no association between HP infection and an increased risk for cardiovascular diseases or mortality.

Subjects with atherosclerosis had higher prevalences of diabetes mellitus and cigarette smoking compared with subjects without signs of atherosclerosis. Multivariate analysis demonstrated no association between atherosclerosis and HP infection, peptic ulcer disease or IgG anti-HP antibodies.

Since the associations of vascular risk factors with vascular diseases tend to be stronger in younger than in older individuals, our findings on an elderly population known to have a high prevalence of both HP infection [29] and atherosclerotic lesions [30], indirectly demonstrated that the recruitment biases were minimal—possibly because all subjects, with or without atherosclerosis, were recruited from the same population of dyspeptic elderly patients. Future studies are needed on a more heterogeneous population: risk factors may surface that are not evident in this elderly subgroup.

In conclusion, those elderly dyspeptic patients who had upper gastrointestinal endoscopy and were found to have gastric HP infection had more peptic ulcer disease but no more atherosclerotic lesions than HP-negative subjects. Patients with vascular ultrasonography-documented atherosclerosis of extracranial cerebral arteries and leg arteries had a higher prevalence of diabetes mellitus, hypertension and cigarette smoking but not HP infection. These results suggest that in elderly subjects with dyspepsia an association of HP infection and extracardiac atherosclerosis is unlikely.

**Key points**

- Elderly dyspeptic subjects with gastric *Helicobacter pylori* infection had more peptic ulcer disease but no more atherosclerotic lesions than *H. pylori*-negative subjects.
- Atherosclerosis of extracranial cerebral and leg arteries was associated with diabetes mellitus, hypertension and cigarette smoking but not with *H. pylori* infection.
- In older people with dyspepsia an association between *H. pylori* infection and extracardiac atherosclerosis is unlikely.

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**References**


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